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Cardiorespiratory fitness is not associated with risk of venous thromboembolism: a cohort study

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ABSTRACT

Objectives. The inverse and independent association between cardiorespiratory fitness (CRF) and arterial thrombotic disease is well established. However, the potential association between CRF and venous thromboembolism (VTE) is not well known. We aimed to assess the prospective association of CRF with the risk of VTE. *Design.* Cardiorespiratory fitness, as measured by maximal oxygen uptake (VO_{2max}), was assessed using a respiratory gas exchange analyser in 2,249 men aged 42-61 years without a history of VTE at baseline in the Kuopio Ischemic Heart Disease prospective cohort. Cox-regression models were used to calculate hazard ratios (HR) with 95% confidence interval (CI) for VTE. We corrected for within-person variability in CRF levels using data from repeat measurements taken several years apart. *Results.* There were 144 (6.4%) incident VTE events recorded during a median follow-up of 25.2 years. The age-adjusted regression dilution ratio of CRF was 0.58 (95% CI: 0.53 to 0.64). The risk of VTE did not decrease per 1 standard deviation increase in CRF in age-adjusted analysis (HR 0.90; 95% CI 0.75–1.08). The association remained consistent on analyses adjusted for several established and emerging risk factors (HR 0.90; 95% CI 0.73–1.12). The corresponding adjusted HRs were 0.80 (95% CI: 0.52-1.23) and 0.82 (95% CI: 0.51-1.32) respectively, when comparing the extreme tertiles of CRF levels. *Conclusions.* In a middle-aged Caucasian male population, CRF was not associated with future risk of VTE. Further studies in women and other age-groups are required to confirm and to generalize these findings.

KEYWORDS

cardiorespiratory fitness; maximal oxygen uptake; venous thromboembolism; cohort study

Introduction

Venous thromboembolism (VTE) (comprising deep vein thrombosis (DVT) and pulmonary embolism (PE)), which is associated with substantial morbidity, high economic costs and premature mortality [1,2], constitutes a substantial public health burden and is a preventable health condition. Venous thromboembolism is closely linked to atherosclerotic cardiovascular disease (CVD) and evidence suggests both conditions share some common risk factors [3,4]. Though both disease states have historically been viewed as two distinct diseases [5], they share common characteristics such as coagulation and platelet activation, hence they may have common pathophysiological mechanisms [6]. The inverse and independent relationship between regular physical activity and arterial thrombotic disease is well established [7-9]. Till recently, evidence on the association between physical activity and the risk of VTE was divergent. In a pooled meta-analysis of 14 prospective cohort studies, we have shown that regular physical activity is associated with reduced risk of VTE [10]. Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake (VO_{2max}), is the gold standard for assessing aerobic capacity and is an index of habitual physical activity [11]. Like physical activity, CRF has also been consistently shown to be independently and inversely associated with vascular outcomes [12]. Given the overall evidence, we postulated that CRF may be linked to the risk of VTE. In this context, we aimed to assess the prospective association of CRF with risk of VTE, using a population-based prospective cohort of 2249 middle-aged Caucasian men.

Methods

The current analysis is based on the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a general population-based prospective cohort study comprising of middle-aged men aged 42-61 years who were recruited from Kuopio in eastern Finland. Study design, recruitment methods and assessment of risk markers have been described previously [13]. The actual baseline cohort consisted of 2,682 participants who had baseline measurements performed between March 1984 and December 1989. In the current

analysis, complete information on CRF, relevant covariates, and VTE outcomes was available for 2,249 men. Written informed consent was obtained from all participants and the research protocol was approved by the institutional review board of the University of Eastern Finland and all study procedures were conducted according to the Declaration of Helsinki. Maximal oxygen uptake (VO_{2max}) was used as a measure of CRF and was estimated using a respiratory gas exchange analyzer during cycle ergometer exercise tests. A detailed description of the measurement of VO_{2max} has been reported previously [14]. As a result of measurement errors in exposure estimation, lifestyle changes, and aging in prospective cohort studies, analysis using only baseline measurements of an exposure could underestimate the true strength of any association between exposure and outcome (i.e. "regression dilution bias"[15]). To clarify this issue, using repeat measurements of repeat measurements of VO_{2max} 11 years apart in a random subset of 565 men, we estimated and corrected for the effect of this regression dilution bias. We included all first lifetime VTE events that occurred from study enrollment through to 2017. These were identified by computer linkage to the National Hospital Discharge Registry data and a comprehensive review of available hospital records. The diagnosis of DVT or PE required positive imaging tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard models after confirming the assumptions of proportionality of hazards.[16] We selected covariates based on their potential as confounders as a result of their known associations with VTE outcomes and observed associations with CRF using the available data[17] and evidence from previous research.[13]All statistical analyses were conducted using Stata version 15 (Stata Corp, College Station, Texas).

Results

The baseline characteristics of study participants are presented in **Table 1**. The mean [standard deviation (SD)] age, BMI, and CRF of 2,249 study subjects at baseline were 53 (5) years, 26.9 (3.5) kg, and 30.2 (8.0) mL/(kg.min) respectively. During a median (interquartile range) follow-up of 25.2 (18.0-27.1) years, a total of 144 VTE cases (annual rate 2.72/1,000 person-years at risk; 95% CI: 2.31 to 3.21) were

recorded. The HR for VTE per 1 SD increase in CRF in analysis adjusted for age was 0.90 (95% CI: 0.75 to 1.08), which remained consistent in analyses adjusted for established risk factors (systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, triglycerides, lipid medication, total physical activity, alcohol consumption, prevalent cancer, and high sensitivity C-reactive protein) 0.90 (95% CI: 0.73 to 1.12) (**Table 2**). The corresponding adjusted HRs were 0.80 (95% CI: 0.52 to 1.23) and 0.82 (95% CI: 0.51 to 1.32) respectively, when comparing the extreme tertiles of CRF levels. The overall age-adjusted regression dilution ratio of CRF was 0.58 (95% CI: 0.53 to 0.64), which suggests that if there was a significant association between CRF and VTE, using one-off or baseline measurements of CRF could under-estimate the risk by [(1/0.58)-1]*100 = 72%. The HRs were more extreme after correction for within-person variability in CRF levels (**Table**).

Discussion

Previous observational cohort data supports an inverse association between CRF and arterial thrombotic disease [12]. To the best of our knowledge, this is the first study to examine the prospective association between objectively measured CRF and risk of VTE in a general population-based cohort of middle-aged Caucasian men. Our results demonstrate no evidence of an association between CRF and future risk of VTE, either in analysis using CRF as a continuous or categorical variable.

Given the close link between atherosclerotic CVD and VTE [6], the established relationship between CRF and atherosclerotic CVD,[12] CRF being an objective index of habitual physical activity, and the fact that both disease entities conditions share physical inactivity as a common risk factor [10], these findings may seem unexpected. Though regular physical activity leads to improved CRF, genetic as well as several other environmental factors influence CRF levels. Evidence suggests that approximately half of the variation in CRF is attributed to heritable factors, with the contribution of inherited factors to the response of CRF to physical activity approximating 45-50% [18]. The level of CRF also depends on several other factors such as baseline health and fitness status, type, duration, and intensity of physical

activity.[18] Hence the null association observed between CRF and VTE may reflect important pathophysiologic differences between CRF and physical activity in the pathogenesis of VTE. There is also a possibility that the null findings may not be due to a true association but could be related to factors such as (i) age, sex, or genetic background of the population; (ii) long follow-up duration; (iii) low statistical power due to low VTE event rates, as VTE is not necessarily a common outcome in middle-aged men; and (iv) VTE occurrence due to factors such as cancer and fractures, which are not related to CRF levels. Due to the absence of previous studies conducted on the topic, larger-scale studies are warranted to confirm or refute these findings. More specifically, other age-groups and women should be targeted in the future.

Several strengths of this study deserve mention and these include novelty, the large sample size, the prospective cohort design, the representativeness of the sample in the general population, the long-term follow-up and repeat measurements of directly assessed CRF allowing for quantification of regression dilution. Limitations included the inability to generalise the results to women and other populations, data was available on only total VTEs which precluded the ability to evaluate specific VTE outcomes (DVT or PE), and the relatively low VTE event rate.

Conclusions

In a middle-aged Caucasian male population, CRF was not associated with future risk of VTE, suggesting that CRF may not play an important role in the pathogenesis of VTE. Furthermore, there may be important pathophysiologic differences between physical activity and CRF in the pathogenesis of VTE. The relationship between CRF and VTE warrants further investigation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Table 1. Baseline participant characteristics overall and by tertiles of cardiorespiratory fitness

	Overall (N=2,249) Mean (SD) or median (IQR) or n (%)	**Tertile 1 (N=750) Mean (SD) or median (IQR) or n (%)**	**Tertile 2 (N=750) Mean (SD) or median (IQR) or n (%)**	**Tertile 3 (N=749) Mean (SD) or median (IQR) or n (%)**
CRF (mL/(kg.min))	30.2 (8.0)	21.7 (4.0)	30.0 (1.8)	39.0 (5.0)
Questionnaire/Prevalent conditions				
Age at survey (years)	52.9 (5.1)	55.0 (4.1)	52.9 (4.8)	50.7 (5.4)
Alcohol consumption (g/week)	32 (6-92)	32 (6-94)	34 (6-100)	30 (7-83)
History of diabetes	79 (3.5)	48 (6.4)	21 (2.8)	10 (1.3)
Current smokers	699 (31.1)	280 (37.3)	234 (31.2)	185 (24.7)
History of CHD	534 (23.7)	322 (42.9)	137 (18.3)	75 (10.0)
History of cancer	35 (1.6)	11 (1.5)	10 (1.3)	14 (1.9)
Lipid medication	13 (0.6)	10 (1.3)	2 (0.3)	1 (0.1)
Physical measurements				
BMI (kg/m^2)	26.9 (3.5)	28.3 (3.8)	26.9 (3.2)	25.5 (2.7)
SBP (mmHg)	134 (17)	136 (19)	135 (17)	131 (14)
DBP (mmHg)	89 (10)	90 (11)	90 (11)	87 (9)
Total physical activity (kcal/day)	287 (150-473)	259 (128-428)	282 (148-462)	321 (181-510)
Lipid markers				
Total cholesterol (mmol/l)	5.91 (1.07)	6.00 (1.09)	5.94 (1.07)	5.79 (1.05)
HDL-C (mmol/l)	1.29 (0.30)	1.22 (0.28)	1.28 (0.30)	1.38 (0.31)
Triglycerides (mmol/l)	1.09 (0.79-1.54)	1.27 (0.92-1.78)	1.10 (0.82-1.55)	0.92 (0.69-1.29)
Metabolic and inflammatory markers				
Fasting plasma glucose (mmol/l)	5.33 (1.20)	5.60 (1.58)	5.30 (0.99)	5.10 (0.86)
Fibrinogen (g/l)	2.96 (2.62-3.32)	3.15 (2.79-3.54)	2.96 (2.63-3.29)	2.81 (2.51-3.14)
High sensitivity CRP (mg/l)	1.24 (0.69-2.36)	1.72 (0.92-3.68)	1.31 (0.77-2.29)	0.84 (0.51-1.57)

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; VTE, venous thromboembolism

Table 2. Association between cardiorespiratory fitness and risk of venous thromboembolism

CRF (mL/(kg.min))	Events/ Total	Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline CRF					
Per 1 SD increase	144 / 2,249	0.90 (0.75 to 1.08)	0.26	0.90 (0.73 to 1.12)	0.34
T1 (6.36-26.86)	47 / 750	ref		ref	
T2 (26.87-33.24)	52 / 750	0.96 (0.65 to 1.44)	0.85	0.99 (0.65 to 1.49)	0.95
T3 (33.25-65.40)	45 / 749	0.80 (0.52 to 1.23)	0.31	0.82 (0.51 to 1.32)	0.43
Usual CRF*					
Per 1 SD increase	144 / 2,249	0.84 (0.61 to 1.15)	0.26	0.84 (0.58 to 1.21)	0.34
T1 (6.36-26.86)	47 / 750	ref		ref	
T2 (26.87-33.24)	52 / 750	0.94 (0.47 to 1.86)	0.85	0.98 (0.48 to 2.00)	0.95
T3 (33.25-65.40)	45 / 749	0.68 (0.32 to 1.43)	0.31	0.72 (0.32 to 1.62)	0.43

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; SD, standard deviation; T, tertile

*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")

Model 1: Adjusted for age

Model 2: Model 1 plus systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, total cholesterol, triglycerides, lipid medication, total physical activity, alcohol consumption, prevalent cancer, and high sensitivity C-reactive protein